Update on Asthma Pharmacotherapy

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Relevance of Chronic Airway Inflammation to Asthma Therapy

- Inflammation is a early and persistent component of asthma
- Preliminary evidence suggests early intervention with anti-inflammatory therapy may modify the disease process
- Studies show improvements in asthma control achieved with inhaled corticosteroids are associated with improvements in markers of airway inflammation

Executive Summary of the NAEPP Expert Panel Report June 2002

Pharmacologic Therapy of Asthma

Chronic Use of Inhaled Corticosteroids Improve Long Term Asthma Outcomes

- Strong evidence from clinical trials show that ICS improve the control of all severity levels of persistent asthma
  - Better pre-bronchodilator FEV_1
  - Reduced bronchial hyperresponsiveness
  - Improved symptom scores and frequency
  - Fewer courses of systemic steroids
  - Reduced urgent care and hospitalization

Chronic Use of Inhaled Corticosteroids Improve Long Term Asthma Outcomes

- Other control medications
  - Long acting B2 agonists (Salmeterol / Fomoterol)
  - Inhaled NSAID (Cromolyn / Nedocromil)
  - Theophylline
  - Leukotriene receptor agonists (Montelukast)
- None are as effective as ICS for improving asthma outcomes
- Studies comparing medications in children under 5 years of age are not available; recommendations are based on expert opinion and extrapolation from studies in older children and adults

Inhaled Corticosteroids

- Beclomethasone diproprionate (Beclovent/ Vanceril)
- Triamcinolone acetonide (Azmacort)
- Flunisolide (Aerobid)
- Fluticasone proprionate (Flovent)
- Budesonide (Pulmicort)

Inhaled Corticosteroids Indications/ Mechanisms

- Long-term prevention of symptoms, control, and reversal of inflammation
- Reduce the need for oral steroids
- Block late phase reaction to allergen and reduce airway hyperresponsiveness
- Inhibit cytokine production, adhesion protein activation, inflammatory cell migration & activation, and microvascular leakage
- Reverse B_2-receptor down-regulation

Inhaled Corticosteroids
Potential Adverse Effects

- Cough, dysphonia, and oral thrush
- High dose can see systemic effects: adrenal suppression, osteoporosis, linear growth suppression, easy bruisability

Barnes PJ. Inhaled Glucocorticoids for Asthma. NEJM 1995; 332:868-875

Kamada AK, et al. Issues in the Use of Inhaled Glucocorticoids. AJRCCM;

Inhaled Corticosteroids and Linear Growth in Children

- Potential risk are well balanced by their benefit
- Growth rates are highly variable in children, short-term changes may not predictive of final adult ht
- Poorly controlled asthma will delay growth
- Children with asthma tend to have longer periods of reduced growth rates prior to puberty
- Low-moderate doses (200-800 mcg/day) have little risk, doses > 800 mcg/day greater potential risks
- High doses of ICS in children with severe persistent asthma, less risk than systemic corticosteroids

Effect of Long-term Treatment with Inhaled Budesonide on Adult Height in Children with Asthma

- Prospective study, non-randomized
- 211 children: 142 treated with budesonide (BUD), 18 controls with asthma – no ICS, 51 healthy siblings were recruited to serve as controls due to high dropout of original control group
- Clinic visits every 6 months; patient diaries completed
- Primary Endpoint: measured vs. target adult height
- BUD treatment mean of 9.2 years; mean daily dose 412 mcg
- Same 2 physicians and 3 nurses saw and measured all children

Agertoft L, Pedersen S. *N Engl J Med*

Results

- No significant difference in final adult height between treatment groups
- No significant correlation between measured and target adult height and the following
  - Treatment duration (P=0.16)
  - Cumulative BUD dose (P=0.14)
  - Sex (P=0.30)
  - Age at study onset (P=0.13)
  - Age of adult height attainment (P=0.82)
  - Duration of asthma at study onset (P=0.37)

Agertoft L, Pedersen S. *N Engl J Med* 2000;343:1064-1069

Inhaled Corticosteroids
Adverse Effects

- **Bone Metabolism/Osteoporosis**
  - Studies complicated by oral steroids and small numbers
  - Clinical implications for risk of osteoporosis and fractures after long-term use are still unknown
  - Low- medium dosing (200-800 mcg/day) seems safe, dose-dependent reduction in bone mineral content
  - Risk of of uncontrolled asthma limiting patient's mobility & activity weighed against use of ICS
  - Concurrent treatment with calcium and Vit D

Inhaled Corticosteroids Adverse Effects

- Disseminated *Varicella*
  - High dose ICS present theoretical risks similar to systemic CS, reports are rare and causality unclear
  - Children who require episodic systemic CS and not had clinical Varicella should receive Varicella vaccine
  - Children on immunosuppressive doses of systemic CS (> 20 mg/day) for more than a month must be steroid free for 1 month prior to vaccine
  - Vaccination after short burst of prednisone is ok
  - VZIG and oral acyclovir for immunosuppressed, varicella naive asthmatics upon exposure
  - Should clinical varicella develop > IV acyclovir

Inhaled Corticosteroids
Adverse Effects

- Hypothalamic-Pituitary-Adrenal Axis (HPA)
  - Issue is complex and requires further study
  - Conflicting data in literature concerning suppression of cortisol production
  - At high doses there is a dose-dependent effect on different measures of HPA function
  - Clinical significance of suppression is not known

Inhaled Corticosteroids Therapeutic Issues

- Spacer/holding chamber devices and mouth rinsing after use decrease local side effects and systemic absorption
- Preparations not interchangeable on mcg or per puff basis. Newer delivery devices will further confuse issue
- Risks of uncontrolled asthma should be weighed against the limited risks of inhaled corticosteroids
- Potential, but small risk of adverse events is well balanced by efficacy

Systemic Corticosteroids Indications / Mechanism

- Short-term (3-10 days) “burst” to gain prompt control of inadequately controlled persistent asthma
- Long-term prevention of symptoms in severe persistent asthma
- Mechanism of action same as inhaled

Systemic Corticosteroids Potential Adverse Effects

- Short-term use : increased appetite, blood glucose, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of femur

- Long-term use : HPA axis suppression, growth suppression, hypertension, dermal thinning, diabetes, cataracts, muscle weakness, rarely impaired immune function

Systemic Corticosteroids Therapeutic Issues

- Use lowest effective dose, for long-term use alternate-day am dosing produces least toxicity

- One study shows improved efficacy with no increase in adrenal suppression when administered at 3 pm rather than in the morning

Beam WR. Timing of prednisone and alterations in airways
in nocturnal asthma. Am Rev Respir Dis 1992; 146:1524-30

Cromolyn and Nedocromil Indications / Mechanisms / Side Effects

- Long-term prevention of sxs, may modify inflammation
- Preventive treatment prior to exposure to exercise or known allergen
- Blocks early and late reaction to allergen, interferes with chloride channel function, stabilizes mast cell membranes and inhibits activation and release of mediators from eosinophils & epithelial cells
- 20 % of patients complain of unpleasant taste from nedocromil

Inhaled Long Acting Beta$_2$-Agonists
Indications / Mechanisms

- Long-term control of sxs, esp. nocturnal sxs, added to anti-inflammatory therapy
- Prevention of EIB
- Not to be used to treat acute symptoms or exacerbations
- Smooth muscle relaxation by increasing cyclic AMP levels
- May inhibit mast cell mediator release, decrease vascular permeability, and increase mucociliary clearance

Inhaled Long Acting Beta$_2$ Agonists
Potential Adverse Effects/ Therapeutic Issues

- Tachycardia, skeletal muscle tremors, hypokalemia, prolongation of QTc interval in overdose
- Not for acute sxs or exacerbations
- Should not be used in place of anti-inflammatory therapy
- May provide more effective sxs control when added to standard doses of inhaled corticosteroid compared to increasing the corticosteroid dose

Theophylline
Indications/ Mechanism/ Side Effects/ Issues

- Long-term control, esp nocturnal sxs
- Smooth muscle relaxation by inhibiting phosphodiesterase, increases diaphragmatic contraction and mucocilliary clearance
- Dose-related acute toxicity's: tachycardia, N & V, CNS stimulation, tachyarrhythmias, seizures, etc.
- Narrow therapeutic range, individual variations in metabolism, affected by numerous factors
- Generally not recommended for exacerbations

Leukotriene Modifiers Indications/Mechanism/Adverse Effects

- Long-term control and prevention of sxs in mild persistent asthma for patients > 12 months old
- Leukotriene receptor antagonists (Accolate and Montelukast) selective competitive inhibitor of LTD_4 & LTE_4 receptors
- Exact roll in long-term management evolving, may be used a steroid sparing agent in some patients

Quick Relief Medications

- Short-acting beta$_2$-agonists
  - Albuterol
  - Terbutaline
- Anticholinergics
  - Ipratropium bromide
- Systemic corticosteroids
  - Prednisone
  - Prednisolone
  - Methylprednisolone

Short Acting $Beta_2$- Agonists

Indications/Mechanism/Adverse Effects/Issues

- Relief of acute sxs, preventive treatment before exercise
- Smooth muscle relaxation by ^ cAMP causes functional antagonism of bronchoconstriction
- Tachycardia, tremor, hgypokalemia, headache, hyperglycemia
- Drug of choice for acute bronchospasm, frequent use is indication for anti-inflammatory therapy
- Regular scheduled daily use <u>is not</u> recommended

Anticholinergics
Indications/Mechanism/Adverse Effects/Issues

- Relief of acute bronchospasm
- Competitive inhibition of muscarinic cholinergic receptors, reduces intrinsic vagal tone to airway, may block reflex bronchoconstriction secondary to irritants or GER esophagitis, decrease mucus secretion
- Dry mouth and respiratory secretions, blurred vision if sprayed in eye
- Reverses only cholinergic bronchospasm, not for EIB, additive effects when given with albuterol

Corticosteroids
Indications/Mechanism/Adverse Effects/Issues

- Moderate to severe exacerbations,reverse inflammation, speed recovery, reduce rate of relapse

- Short-term use continues until PEF> 80% PB or sxs resolve, usually 3-10 days.

Soothing Parents Qualms About ICS

- Typical prednisone burst for asthma exacerbation is 40 mg /day for 5 days
- 200 mg = 200,000 ug (all bioavailable)
- Equivalent to:
  - 200 days Pulmicort Respules, 0.5 mg BID
  - 400 days Pulmicort Respules, .25 mg BID
  - 500 days Azmacort, 200 ug BID
  - 454 days Flovent, 220 ug BID
  - 400 days Advair, 250/50 ug BID
- Only 1-6% of ICS bio-available

Aerosol Delivery

- Efficacy of bronchodilators and ICS result from topical effects in airway
- Benefits of inhaled therapy
  - Rapid onset of action
  - Increased safety
  - Reduced drug usage
  - Cost-effective
- NHLBI 97’ endorsed use of masked holding chamber

Poor Inhalation Technique Even After Instruction in Children with Asthma

- 66 newly referred children with asthma
  - 60 / 66 had received instruction from PCP
  - 58% performed all steps correctly
  - 97% thought they had proper technique
- 29 control patients followed in asthma clinic
  - 93% performed all steps correctly
- Major difference was extent of training
  - PCP relied on verbal instruction for 5 mins
  - Asthma clinic used demonstration til correct (30 mins)

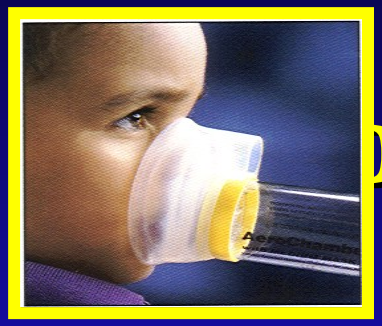
Kamps AWA, et al. Pediatr Pulmonol 2000;29:39

pMDI +Valved Holding Chamber

- Most studies report equal or better efficacy and less side effects
- Improved patient adherence to therapy
- Immediate use with little preparation
- Can be used in many settings
- Treatment effect can be titrated
- Significant cost benefit

Small Volume Nebulizer

- Less dependent on patient cooperation
- Expensive
- Time consuming
- Bulky and unwieldy + paraphernalia
- Dependent on power source
- Risk of infection spread
- Intra-device and inter-device variability
- Increased risk of side effects



Strategies for Masked Aerochamber Treatments in the Toddler

- Let the child play with the Aerochamber
- DO NOT force the mask on the child
- Make the experience fun
- Treatment while they are doing fun things
- Stickers on the Aerochamber

Strategies for Masked Aerochamber Treatments in the Toddler

- Practice short “pretend” treatments
- Give high praise and rewards
- Treatments to teddy bears, dolls, parent
- Last resort administer while asleep

Monitor Pharmacotherapy

- Adherence to controller regimen
- Inhaler technique
- Usage of as-needed B_2-agonists
- Frequency of oral steroid “ bursts “
- Changes in dosage of inhaled corticosteroids or other long-term controller medications
- Side effects of medication

Executive Summary of the NAEPP Expert Panel Report

June 2002

Stepwise Approach for Managing Asthma in Adults and Children

Classification of Asthma Severity

Clinical Features before Treatment

Mild Intermittent (Step 1)

- Symptoms < 2 times/week
- Asymptomatic and normal PF between exacerbations
- Exacerbations brief (few hrs-days), variable intensity
- Nocturnal sxs < 2/ month
- FEV_1 or PEF > 80% predicted
- PEF variability < 20%

Classification of Asthma Severity

Clinical Features before Treatment

Mild Persistent (Step 2)

- Symptoms > 2 times/ week, but < 1 time/day
- Exacerbations may affect activity
- Nocturnal sxs > 2 times/month
- FEV_1 or PEF > 80 % predicted
- PEF variability 20-30 %

Classification of Asthma Severity

Clinical Features before Treatment

Moderate Persistent (Step 3)

- **Daily symptoms**
- **Daily use of of inhaled short-acting beta$_2$-agonist**
- **Exacerbations affect activity**
- **Exacerbations > 2 times/week, may last days**
- **Nocturnal sxs > 1 time/week**
- **FEV_1 or PEF between 60-80 % predicted**
- **PEF variability > 30 %**

Classification of Asthma Severity

Clinical Features before Treatment

Severe Persistent (Step 4)

- Continual Symptoms
- Limited physical activity
- Frequent exacerbations
- Nocturnal sxs frequent
- FEV1 or PEF < 60 % predicted
- PEF variability > 30 %

Classifying Asthma Severity

Classification of Asthma Severity: Clinical Features Before Treatment

	Days With Symptoms	Nights With Symptoms	PEF or FEV_1*	PEF Variablity
Step 4 Severe Persistent	Continual	Frequent	≤60%	>30%
Step 3 Moderate Persistent	Daily	≥5/month	>60%- <80%	>30%
Step 2 Mild Persistent	3-6/week	3-4/month	≥80%	20-30%
Step 1 Mild Intermittent	≤2/week	≤2/month	≥80%	<20%

* Percent predicted values for forced expiratory volume in 1 second (FEV_1) and percent of personal best for peak expiratory flow (PEF) (relevant for children 6 years old or older who can use these devices).

NOTES:

- Patients should be assigned to the most severe step in which *any* feature occurs. Clinical features for individual patients may overlap across steps.
- An individual's classification may change over time.
- Patients at any level of severity of chronic asthma can have mild, moderate, or severe exacerbations of asthma. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.
- Patients with two or more asthma exacerbations per week (i.e., progressively worsening symptoms that may last hours or days) tend to have moderate-to-severe persistent asthma.

Goals of Long Term Treatment

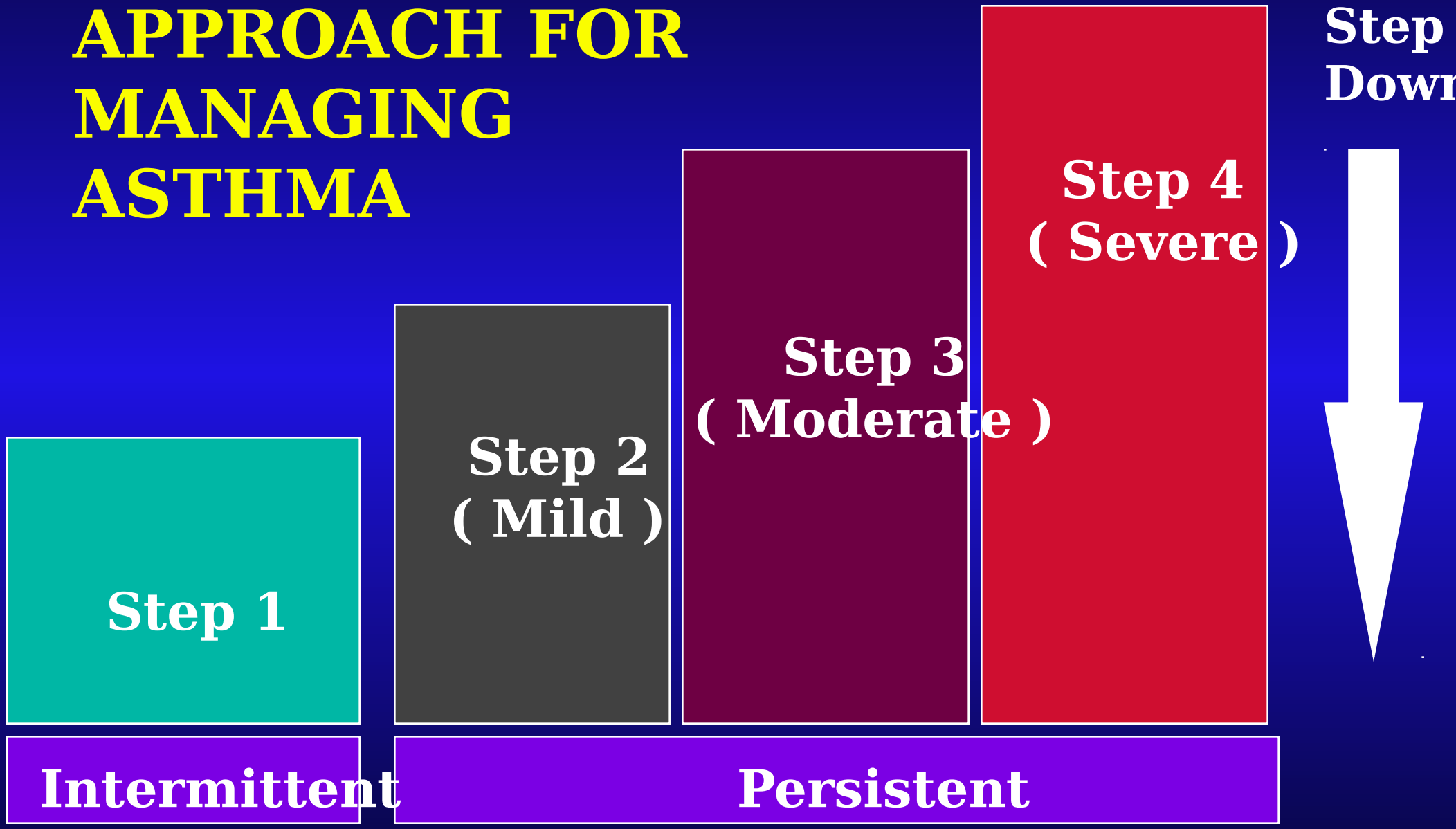
- Preventing chronic and troublesome symptoms
- Maintaining “ normal” pulmonary function
- Maintaining normal activity levels (including exercise and other physical activities)
- Preventing recurrent exacerbations and minimizing ED visits and hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meeting patient’s and families expectations of and satisfaction with asthma care

Gaining Control of Asthma

Stepwise Approach

- Clinician must judge individual patient needs and circumstances to determine what step to initiate therapy
- Two approaches to gaining control:
  - Start treatment at appropriate severity step and increase if control not achieved
  - Administer therapy at a level higher than the patient's step of severity to gain rapid control, then step down once control achieved
  - The more aggressive approach of gaining prompt control is preferred by the Expert Panel

STEPWISE APPROACH FOR MANAGING ASTHMA



Stepwise Approach

- General guidelines, not intended to be rigid, needs to be tailored to needs of individual pt
- A rescue course of systemic corticosteroids may be needed at any time and at any step
- Even patients with intermittent asthma can experience severe and life-threatening exacerbations requiring systemic corticosteroids
- At each step environmental control measures required

Step 1(Mild Intermittent) Treatment

- No daily medications needed
- Quick relief with short-acting inhaled beta$_2$-agonist as needed for symptoms
- Intensity of treatment will depend on severity of exacerbation
- Use of short-acting beta$_2$-agonists more than 2 times/week may indicate the need to initiate long term control therapy

Step 2 (Mild Persistent) Treatment

- Long-Term control with one daily medication
  - Preferred treatment is low dose ICS
  - Alternative treatments listed alphabetically:
    - Cromolyn
    - Leukotriene modifier
    - Nedocromil
    - Theophylline
- Quick relief/rescue with short-acting beta$_2$-agonist, ^ use indicates need for additional long-term therapy

Step 3 (Moderate Persistent) Treatment

- Daily control medication
  - Preferred treatmnet is low-medium dose of ICS plus long acting B_2 agonist
  - Alternative treatments
    - Increased ICS within medium dose range, and add LABA
    - Increased ICS in medium dose range and add either leukotriene modifer or theophylline
  - Inhaled Corticosteroid (low-medium dose) and add a long-acting bronchodilator, esp. for nocturnal sxs
- Quick relief/rescue with short-acting beta$_2$-agonist

Step 4 (Severe Persistent) Treatment

- **Daily control medication:**
  - **Preferred treatment is high dose ICS and LABA and if needed:**
    - **Leukotriene modifier**
    - **Systemic Corticosteroids, 2 mg/kg/day not exceeding 60 mg/day**
- **Quick relief/rescue with short-acting beta$_2$-agonist**

Usual Pediatric Doses (mcg) for Inhaled Corticosteroids

Drug	Low	Medium	High
BDP(42 ug/p)	84-336	336-672	> 672
Flun(250 ug/p)	500-750	1,000-1,250	>1,250
TAM(100 ug/p)	400-800	800-1,200	>1,200
FP(44/110/220/p)	88-176	176-440	>440
BUD(200ug)	100-200	200-400	>400

BDP- Beclomethasone dipropriate, Flun- Flunisolide, BUD
TAM- Triamcinolone, FP-Fluticasone proprionate,

Managing Special Situations in Asthma

- **Seasonal Asthma**
  - Symptoms only due to certain pollens and molds
  - Treated by stepwise approach
  - Consider daily long-term anti-inflammatory therapy during the season
- **Cough Variant Asthma**
  - Seen especially in young children with cough at night
  - Monitoring of am/pm PEF variability and/or therapeutic trial
  - Once dx made treat according to stepwise approach

Exercise-Induced Bronchospasm (EIB)

- Should be anticipated in all asthma patients
- Bronchospastic event caused by a loss of heat, water, or both from the airway during exercise
- Hyperventilation results in cooler, dryer air
- Occurs during or minutes after vigorous exercise, reaches peak 5-10 after, resolves in 20-30 mins.
- Exercise maybe only precipitant of asthma sxs in some pts.
- Monitor these pts closely to ensure no sxs other times

Exercise-Induced Bronchospasm (EIB)

- EIB is often a marker of inadequate asthma management and responds well to regular anti-inflammatory therapy
- Diagnosis by exercise challenge, > 15% drop in FEV_1
- Goal of management is for full participation in any activity without sxs, should not limit activities
- Recommended treatments include:
  - Short-acting beta2-agonists shortly before exercise
  - Salmeterol will prevent EIB for 10-12 hours
  - Cromolyn/Nedocromil before exercise
  - Long-term anti-inflammatory medication